At the outset, it is noted that new independent Claims 117, 130, 134 and 145 are supported by the original claims as filed as well as by page 9, lines 19-20 of the present specification. Claims 119, 136 and 149 clarify that the crystallographic and NMR data relate to the 19 kilodaltan C-terminal fragment of the MSP-1 protein. See pages 37-47 of the present specification.

Claims 68 -116 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting over Claims 1-19 and 43 of co-pending Application Serial No. 09/125,031 and Claims 1 to 14, 37 and 38 of co-pending Application Serial No. 09/125,032. For the following reasons, this rejection is respectfully traversed.

First, U.S. Patent Application Serial No. 09/125,032 has been expressly abandoned. Therefore, this ground of rejection is moot.

Second, as to S.N. 09/125,031, a Restriction Requirement was issued in both that and the present application. In the present application, Applicants elected the Group I claims drawn to proteins. In U.S. Application Serial No. 09/125,031, nucleic acid and vectors were elected.

Therefore, the present invention is clearly patentably distinct from the elected subject matter in SN 09/125,031. This is evidenced by Paper No. 8 of the present application, i.e. a Restriction Requirement[1] issued August 31, 1999. The Examiner deemed therein that the protein claims and the vector and nucleic acid claims were considered patentably distinct. Otherwise the Requirement would not have been made.

Therefore, in view of the above, this ground of rejection is deemed moot.

Claims 68-116 stand rejected under 35 U.S.C. §112, first paragraph. For the following reasons, this rejection is respectfully traversed.

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[1] A five-way restriction requirement was made therein.

In essence, the Examiner opines that the specification fails to teach the recombinant proteins as presently claimed and, as such, not in accord with Vas-Cath Inc. v. Mahurkar[2]. Applicants respectfully disagree with the Examiner for the following reasons.

First, 16 to 34 of the specification teach the skilled artisan how to construct the various recombinant proteins of the present invention. Figures 1A, 1B, 1C and 1D illustrate the various recombinant sequences used to make the recombinant proteins of the present invention. Moreover, Figure 2 illustrates that soluble recombinant antigen is produced by the vectors of the present invention (using SDS-PAGE). Thus, the sequences are, in fact, described by their chemical structure in the specification.

Second, one skilled in the art would clearly recognize that the present inventors had possession of the recombinant protein residues, since the specification as well as the articles cited therein clearly illustrate this point.

Third, all that the "written description" requirement of 35 USC 112 requires is that those skilled in the art recognize that Applicants made the invention claimed. Moreover, it is clear from Amgen, Inc. v. Chugai Pharmaceutical Co., 18 USPQ 2d 1016 (Fed. Cir. 1991), that the understanding or level of skill in the pertinent art should also be taken into consideration. In this field of biotechnology, the level of skill is high, actually necessitating less not more disclosure.

Therefore, in view of the above, withdrawal of this rejection is respectfully requested.

Claims 68 to 116 have been rejected under 35 U.S.C. §112, first paragraph for ostensible lack of enablement. For the following reasons, this rejection is respectfully traversed.

In rendering this rejection, the Examiner purports that since the epitopes of the

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[2] See page 4 of the Official Action.

claimed recombinant protein are not defined, the present invention is not enabling. Applicants disagree with this conclusion for the following reasons.

First, it was well known in the art that the C-terminal MSP-1_{19} sequence has two epidermal growth factor-like domains as confirmed by Blackman et al, attached as Annex I. EGF-like domains were structurally known prior to the filing of the present invention as described by cite 22 in the references of Annex I.

The present specification clearly states at least on pages 9 and 41 that these two EGF-like domains form a defined entity which are likely to be essential for the active principal in recombinant analogs. Moreover, Figure 11A, for example, illustrates the backbone of one of the recombinant proteins and the disulfide bridges which are found in the two EGF-like regions. These disulfide bridges are deemed to be important to induce an immune response *in vivo*, which is taught throughout the specification. It was further shown that under reduced conditions, which means that the disulfide bonds are broken, the conformational epitopes are not recognized by human serum and thus do not induce an immune response.

Therefore, the specification clearly teaches that to maintain an immune response the conformational epitopes, which are illustrated with respect to the amino acid positions in, for example, Figure 11A are necessary.

Finally, Figure 4 shows the alignment between *P. vivax* and *P. cynomolgi*. Applicants submit that it would not be undue experimentation to make constructs and test them for the conformational epitopes. See the discussion above regarding the level of skill in this art and the clear implication as well for the "enablement" question posed by the Examiner. Amgen v. Chugai.

Therefore, in view of the above, withdrawal of this rejection is respectfully requested.

Claims 70 and 95 have been rejected under 35 U.S.C. §102(b) as being anticipated by

Shi et al, as evidenced by Egan et al. For the following reasons, this rejection is respectfully traversed.

Certain of the new Claims recite the atomic coordinates in Annexes I, II or III, as well as the NMR fingerprints of Figures 12.0a to 12.2c. The atomic coordinates, as well as the NMR data are for *P. cynomolgi* MSP-1_{19}, *P. vivax* MSP-1_{19} and *P. falciparum* MSP-1_{19}, respectively.

Shi et al relates to three known natural variant forms of the yeast-expressed recombinant 19-kDA fragment of *Plasmodium falciparum* that are referred to as E-KNG, Q-KNG and E-TSR antigens. These variants have either a Q or E in the first EGF-like domain at position 1644 and in the second EGF-like domain, amino acid residues at positions 1691, 1700 or 1701 have been found to be either TSR or KNG.

Shi et al does not disclose recombinant constructs from *P. cynomolgi* MSP-1_{19} or *P. vivax* MSP-1_{19} and therefore this rejection should only apply, at least, with respect to *P. falciparum* MSP-1_{19}.

The Examiner purports that the NMR data and the crystallography data are inherent in the recombinant yeast produced 19-kDa fragment of the MSP-1 antigen. However, the recombinant protein produced in Shi et al does not have the GPI anchor. This is evidenced by Kaslow et al, filed in the last response dated July 24, 2000, as Annex II (hereinafter referred to as old Annex II). More specifically, Kaslow et al states the following at page 286:

> One possible explanation for this apparent inconsistency is that parasite-produced $MSP1_{19}$ is modified by a GPI anchor whereas the $rMSP1_{19}$ is not.

Since $rMSP1_{19}$ stands for the recombinant protein, it is clear that recombinant protein produced in Shi et al does not anticipate previous Claims 70 and 95.

Moreover, a 1996 Abstract (#683) enclosed as new Annex II teaches that the 19 kD

C-terminal fragment from *P. falciparum* MSP-1 did not react with conformational epitope monoclonal antibodies unless the recombinant protein was reduced.

This is in contrast to the claims of the present invention, which recite that the recombinant protein is unstable in a reducing agent.

Therefore, in view of the above, withdrawal of this rejection is respectfully requested.

Claims 70 and 95 have been rejected under 35 U.S.C. §102(b) as being anticipated by Egan et al. For the following reasons, this rejection is respectfully traversed.

Egan et al disclose the relationship between cellular and humoral immune responses to defined epitopes of the C-terminal MSP-1 protein of *Plasmodium falciparum* in immune blood donors

Egan et al does not disclose recombinant constructs from *P. cynomolgi* MSP-1_{19} or *P. vivax* MSP-1_{19} and, therefore, this rejection should only apply, at most, with respect to *P. falciparum* MSP-1_{19}.

Egan et al disclose that T-cell responses in reduced recombinant proteins and linear peptides were more prevalent than responses to disulfide-bonded proteins suggesting that the complex disulfide-bonded structure of native MSP-1_{19} may inhibit antigen processing or presentation. More specifically, the following is stated at page 3025 of Egan et al prior to the heading Materials and Methods:

> In addition, we provide evidence that the structure of MSP-1_{19} with its numerous disulfide bonds, may inhibit antigen processing or presentation and that reduction of the antigen prior to presentation to T cells can, at least *in vitro* significantly enhance its recognition (emphasis added).

This is the exact opposite teaching of the present invention wherein the recombinant 19 C-terminal fragment of MSP-1 is unstable in a reducing medium. Hence, Egan et al teach away from the present invention.

Moreover, the recombinant antigens set forth under Materials and Methods section of Egan et al were the 19-kDA protein produced as a fusion protein in *E. coli* and the MAD20 version of MSP-1_{19} obtained from David Kaslow which was expressed in yeast.

With respect to the protein expressed in *E. coli*, it was well known that such a protein does not form correct disulfide bonds. This fact is evidenced in U.S. Patent 5,720,959, of record, wherein at column 2, lines 10 to 15, the following was stated:

> Since it is a well known observation that proteins expressed as intracellular proteins in *E. coli* do not form correct disulfides...

Therefore, the conformational data obtained from the *E. coli* expressed 19 kDa MSP-1_{19} protein would not be the same as those claimed in the Annexes. This is evidenced by Figure 11A in the present specification where the disulfide bridges were definitely indicated.

Furthermore, with respect to the MAD20 sequence, this was obtained from David Kaslow and was reproduced in yeast. Once again, the Examiner's attention is directed to old Annex II of record wherein it is clearly stated that the rMSP-1_{19} produced in yeast does not have the GPI anchor. The main author of the Annex II publication is David Kaslow.

Moreover, a 1996 Abstract (#683) enclosed as new Annex II teaches that the 19 kD C-terminal fragment from *P. falciparum* MSP-1 did not react with conformational epitope monoclonal antibodies unless the recombinant protein was reduced.

This is in contrast to the claims of the present invention, which recite that the recombinant protein is unstable in a reducing agent.

Therefore, the present invention is clearly not anticipated by Egan et al. Withdrawal of this rejection is respectfully requested.

Claims 70 and 95 have been rejected under 35 U.S.C. §102(b) as being anticipated by Holm et al. For the following reasons, this rejection is respectfully traversed.

Holm et al was published on November 1, 1997, as evidenced by Annex III, which is

less than one year prior to the filing date of the present invention. Therefore, Holm et al does not quality as prior art against the present application under 35 U.S.C. §102(b).

Therefore, withdrawal of this rejection is respectfully requested.

Claims 68 to 116 have been rejected under 35 U.S.C. §102(a) as being anticipated by Chang et al. This rejection is respectfully traversed.

Chang et al disclose a recombinant Baculovirus 42-kilodalton C-terminal fragment from *Plasmodium falciparum* MSP-1 protein and the protection of this 42-kilodalton fragment of *Aotus* monkeys against malaria.

The Examiner purports that Chang et al discloses a 19 kD C-terminal fragment of MSP-1 from *P. falciparum*. However, Chang et al do not disclose that this construct remains anchored to the surface of the *Plasmodium* parasite at the end of its penetration phase into human erythrocytes during an infectious cycle as presently claimed. This is evidenced by the coding region that stops at Ser 1705.

In contrast, in the present specification at least at page 17, the construction stopped at Ile 1726, which gave rise to the GPI anchor.

Further, Chang et al fail to disclose a recombinant protein of *Plasmodium cynomolgi*.

The new claims relating to vaccinating compositions and those claims dependent thereon now recite that the compositions contains alum. As pointed out at least on page 26, the only adjuvant, which is currently allowed in man is alum. Chang et al teach administering their Bv_p42 protein in Freund's adjuvant only. Therefore, the newly presented claims directed to this subject matter are not anticipated by Chang et al.

In view of the above, withdrawal of this rejection is respectfully requested.

Claims 68 to 116 have been rejected under 35 U.S.C. §102(e) as being anticipated by Druihle et al, U.S. Patent 5,690,941.

Druihle et al teach specific peptides that are recognized by antibodies recognizing the sporozoite and hepatic stages of *Plasmodium falciparum*, but do not recognize the blood stage of *Plasmodium falciparum*.

In contrast, the present invention is directed to merozoite form that is the blood stage of the *Plasmodium* parasite.

The Examiner purports that the peptides in Druihle et al inherently comprise a portion of the p19 C-terminal fragment. Applicants totally disagree with this conclusion since Druihle et al explicitly excludes any blood stage peptides, which are encompassed by the claims of the present invention.

Indeed, as set forth in Annex IV, the life cycle of the malaria parasite dictates the type of vaccines that can be used for malaria, i.e., at the sporozoite, merozoite or gamete levels of the life cycle. The sporozoite protective epitope is made up of four amino acids repeated twenty-three times. Hence, it is quite different from the presently claimed merozoite recombinant protein and vaccinating compositions which contain two epidermal growth factor regions. Hence, the peptide described in Druihle et al does not inherently contain the p19-C terminal fragment of MSP-1.

Therefore, in view of the above, withdrawal of this rejection is respectfully requested.

Claims 68 to 116 have been rejected under 35 U.S.C. §102(e) as being anticipated by Holder et al, U.S. Patent No. 5,720,859. For the following reasons, this rejection is respectfully traversed.

Holder et al teach the use of truncated 48 amino acid sequences in isolation from the sequences naturally occurring MSP-1 protein for use as a vaccine against malaria. These sequences encode only the EGF1-like and the EGF2-like domains.

Holder et al fail to teach that the C-terminal fragment remains anchored to the surface

of the *Plasmodium* parasite.

Moreover, Holder et al is not directed to a 19 kDa recombinant protein or vaccinating composition from *Plasmodium cynomolgi*.

Therefore, Claims 68 to 116 are not anticipated by Holder et al. Thus, in view of the above, withdrawal of this rejection is respectfully requested.

Claims 68 to 116 have been rejected under 35 U.S.C. §102(b) as being anticipated by Egan et al (1995). For the following reasons, this rejection is respectfully traversed.

Egan et al disclose the expression of MSP-1_{19} in *E. coli*, as well as in yeast. As proven above, proteins expressed in *E. coli* do not retain the necessary disulfide bridges needed for antigenicity. Hence, the recombinant protein of Egan et al would not induce an immune response and inhibit parasitemia, as recited in the claims.

With respect to the recombinant protein expressed in yeast, the construct that was used in cited as publication 23. Cited publication 23 is Kaslow et al, which was the publication attached as old Annex II in the last filed response. This publication taught the GPI anchor sequence was not present in their recombinant construct.

Moreover, a 1996 Abstract (#683) enclosed as new Annex II teaches that the 19 kD C-terminal fragment from *P. falciparum* MSP-11 did not react with conformational epitope monoclonal antibodies unless the recombinant protein was reduced. It should also be noted that RC Kaslow is an author of this Abstract.

This is in contrast to the present invention, wherein the recombinant protein is unstable in a reducing agent.

Since all of the above elements are missing from the teachings of Egan et al, this reference clearly does not (and could not) teach the presently-claimed invention.

Therefore, in view of the above, withdrawal of this rejection is respectfully requested.

Claims 68-116 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Claims 1-9 and 43 of co-pending application SN 09/125,031 and Claims 1-14 and 37-38 of co-pending application SN 09/125,032. For the following reasons, this rejection is respectfully traversed.

Since SN 09/125,032 has been abandoned and S N 09/125,031 has the same assignee as the present invention, this rejection is not proper in view of 35 U.S.C. §103(c).[3]

Therefore, in view of the above, withdrawal of this rejection is respectfully requested.

Claims 68-116 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Claims 1-19 and 43 of co-pending SN 09/125,031 and Claims 1-14 and 37-38 of co-pending SN. 09/125,032. For the following reasons, this rejection is respectfully traversed.

Since SN 09/125,032 has been abandoned and SN 09/125,031 has the same assignee as the present invention, this rejection is not proper in view of 35 U.S.C. §103(c).

Therefore, withdrawal of this rejection is respectfully requested.

Accordingly, in view of all of the above, it is believed that the present application now stands in condition for allowance. Early notice to this effect is earnestly solicited.

Respectfully submitted,

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[3] 35 USC 103 (c) recites that "[s]ubject matter developed by another person, which qualifies as prior art only under one or more of subsections (e), (f), and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

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Marked-Up Copy
Serial No: 09/134,333
Amendment Filed on:
April 20, 2001

IN THE CLAIMS

Claims 68-116 (Cancelled)
Claims 117-149 (New)

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[13] Scripps charges that Genentech's recombinantly-produced Factor VIII:C infringes the product-by-process claims, either literally or by application of the doctrine of equivalents. The district court remarked that the product-by-process claims would not be infringed unless the same process were practiced. Scripps correctly points out that this statement appears to diverge from our precedent, recognizing that this precedent arose in the context of patent prosecution, not patent infringement. *E.g., In re Thorpe,* 777 F.2d 695, 227 USPQ 964 (Fed. Cir. 1985) (holding that prior art pertinent only to product is proper ground for rejecting product-by-process claims); *In re Brown,* 459 F.2d 531, 535, 173 USPQ 685, 688 (CCPA 1972) (in product-by-process claims the patentability of the product must be established independent of the process); *In re Bridgeford,* 357 F.2d 679, 682 n.5, 149 USPQ 55, 58 n.5 (CCPA 1966) (recognizing that some courts in infringement litigation have construed product-by-process claims as limited to the particular process, but holding that patentability is determined independent of the process). In determining patentability we construe the product as not limited by the process stated in the claims. Since claims must be construed the same way for validity and for infringement, the correct reading of product-by-process claims is that they are not limited to product prepared by the process set forth in the claims. Thus, these claims are subject to an infringement analysis similar to that described in Part V, *ante.* Infringement of the product-by-process claims may be considered at trial.

IX

Attorney Fees

The district court held that this was an exceptional case under 35 U.S.C. §285, apparently due to the court's rulings on inequitable conduct and failure to comply with the best mode. Holdings under §285 are reviewed for abuse of the trial court's discretionary authority, considering the court's findings and conclusions and any other appropriate factors. *See Reactive Metals & Alloys Corp. v. ESM, Inc.,* 769 F.2d 1578, 1583, 226 USPQ 821, 824 (Fed. Cir. 1985). In view of our reversal of the grants of summary judgment on the issues of best mode and inequitable conduct, the award of attorney fees flowing therefrom must be vacated. *See State Indus., Inc. v. A.O. Smith Corp.,* 751 F.2d 1226, 1238, 224 USPQ 418, 426 (Fed. Cir. 1985) (reversing ground for holding case exceptional and accompanying award of attorney fees).

X

Other Issues

We have not repeated all the arguments and issues raised by both sides, including charges of frivolity, misstatement, and worse. Encumbered by the summary nature of the proceedings, neither scientific nor evidentiary truth has risen easily to the surface. However, we *DENY* Scripps motion for sanctions against Genentech for filing a frivolous cross-appeal, for some of the issues raised were not clearly hopeless in law and fact. We also *DENY* each side's motions to strike various materials filed and to dismiss issues raised by the other.

Costs

Each party shall bear its costs.

AFFIRMED IN PART, REVERSED IN PART, VACATED IN PART, AND REMANDED

Court of Appeals, Federal Circuit

Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.

Nos. 90-1273, -1275

Decided March 5, 1991

PATENTS

1. Patentability/Validity — Date of invention — Conception (§115.0403)

Conception of chemical compound requires that inventor be able to define compound so as to distinguish it from other materials, and to describe how to obtain it, rather than simply defining it solely by its principal biological property; thus, when inventor of gene, which is chemical compound albeit complex one, is unable to envision detailed constitution of gene so as to distinguish it from other materials, as well as method for obtaining it, conception is not achieved until reduction to practice has occurred, and until after gene has been isolated.

2. Patentability/Validity — Date of invention — Conception (§115.0403)

Conception of generalized approach for screening DNA library that might be used to identify and clone erythropoietin gene of then-unknown constitution is not conception of "purified and isolated DNA sequence" encoding human EPA, since it is not "definite and permanent idea of the complete and operative invention."

3. Patentability/Validity — Obviousness — Relevant prior art — Particular inventions (§115.0903.03)

Federal district court did not err in holding non-obvious claims for purified and isolated DNA sequence encoding human hormone erythropoietin, in view of evidence showing that procedures may have been obvious to try, but also showing that there was no reasonable expectation of success.

4. Patentability/Validity — Specification — Best mode (§115.1107)

Determination of whether best mode requirement is satisfied is question of fact and thus is reviewed under clearly erroneous standard.

5. Patentability/Validity — Specification — Best mode (§115.1107)

Biological deposit is required to satisfy best mode requirement, for patents involving novel, genetically-engineered biological subject matter, if invention is incapable of being practiced without access to that organism, but if organism is created by insertion of genetic material into cell obtained from generally available sources, then cell deposit itself is not necessary and all that is required is description of best mode and adequate description of means of carrying out invention; if cells can be prepared without undue experimentation from known materials, based on description in patent specification, deposit is not required.

6. Patentability/Validity — Specification — Best mode (§115.1107)

Evidence showing that scientists were unable to duplicate inventor's genetically-heterogeneous best mode cell strain does not demonstrate that best mode requirement is not satisfied, since issue is whether disclosure is "adequate," and exact duplication is not necessary.

7. Patentability/Validity — Specification — Enablement (§115.1105)

Issue of whether claimed invention is enabled under 35 USC 112 is question of law that is reviewed de novo.

8. Patentability/Validity — Specification — Enablement (§115.1105)

Patent applicant is entitled to claim invention generically, if invention is described sufficiently to meet requirements of 35 USC 112; however, applicant, in claims for DNA sequences encoding erythropoietin, which has claimed every possible analog of gene containing about 4,000 nucleotides, but which has provided details for preparing only few EPO analog genes has not provided sufficient disclosure to support its claims, since, in view of structural complexity of EPO gene, manifold possibilities for change in its structure, and uncertainty as to what utility will be possessed by these analogs, additional disclosure is needed as to identifying various analogs within scope of claim, methods for making them, and structural requirements for producing compounds with EPO-like activity.

9. Infringement — Defenses — Fraud or unclean hands (§120.1111)

Ultimate conclusion of inequitable conduct is reviewed under abuse of discretion standard, but underlying factual findings are reviewed under clearly erroneous standard.

10. Patentability/Validity — Specification — Enablement (§115.1105)

Federal district court erred by concluding that patent for method for purification of erythropoietin sufficiently enabled person of ordinary skill in art to obtain homogeneous EPO from natural sources having mean in vivo specific activity of at least 160,000. since court erred in accepting in vitro data as support for claims containing in vivo limitation.

11. Patentability/Validity — Specification — Claim adequacy (§115.1109)

Patent construction — Claims — Definin terms (§125.1305)

Claim whose meaning is in doubt is prop erly declared invalid, especially when there close prior art; thus, federal district court di not err in holding that claim for homoge eous erythropoietin which has specific acti ity limitation of "at least about" 160,000 w indefinite, although such holding does n preclude any and all uses of term "about" patent claims, since such term may be a ceptable in appropriate fact situations.

Particular patents — Chemical Erythropoietin

4,677,195, Hewick and Seehre, meth for the purification of erythropoietin a erythropoietin compositions, claims 1, 3, and 6 invalid.

4,703,008, Lin, DNA sequences encodi erythropoietin, claims 2, 4, and 6 valid a infringed; claims 7, 8, 23-27, and 29 inval

Appeal from the U.S. District Court for the District of Massachusetts, Young, J. (Saris, U.S. magistrate); 13 USPQ2d 1737. Action by Amgen Inc. against Chugai Pharmaceutical Co. Ltd. and Genetics Institute Inc. for infringement of patent no. 4,703,008, to which defendants counterclaimed alleging infringement of patent no. 4,677,195. From federal district court decision holding certain claims of both patents valid and infringed, and holding other claims invalid, parties cross-appeal. Affirmed in part, reversed in part, and vacated in part.

Edward M. O'Toole, Michael F. Borun, Richard A. Schnurr, and Christine A. Dudzik, of Marshall, O'Toole, Gerstein, Murray & Bicknell, Chicago, Ill.; Steven M. Odre and Robert D. Weist, Thousand Oaks, Calif., for Amgen.

Kurt E. Richter, Eugene Moroz, William S. Feiler, and Michael P. Dougherty, of Morgan & Finnegan, New York, N.Y., for Chugai Pharmaceutical.

William F. Lee, William McElwain, Ian Crawford, David Marder, David B. Bassett, and Sarianna T. Honkola, of Hale & Dorr, Boston, Mass., for Genetics Institute.

Before Markey, Lourie, and Clevenger, circuit judges.

Lourie, J.

This appeal and cross appeal are from the March 4, 1990, judgment of the United States District Court for the District of Massachusetts, No. 87-2617-Y, *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 13 USPQ2d 1737 (1990), and involve issues of patent validity, infringement, and inequitable conduct with respect to two patents: U.S. Patent, 4,703,008 ('008), owned by Kirin-Amgen Inc. (Amgen), and U.S. Patent 4,677,195 ('195), owned by Genetics Institute, Inc. (GI).

Chugai Pharmaceutical Co., Ltd. (Chugai) and Genetics Institute, Inc. (collectively defendants) assert on appeal that the district court erred in holding that: 1) Amgen's '008 patent is not invalid under 35 U.S.C. §§102(g) and 103; 2) the '008 patent is enforceable; 3) the failure of Amgen to deposit the best mode host cells was not a violation of the best mode requirement under 35 U.S.C. §112; and 4) claims 4 and 6 of GI's '195 patent are invalid for indefiniteness under 35 U.S.C. §112.

On cross appeal, Amgen challenges the district court's holdings that: 1) claims 1 and 3 of the '195 patent are enabled; 2) the '195 patent is enforceable; 3) this is not an exceptional case warranting an award of attorney fees to Amgen; and 4) claims 7, 8, 23–27 and 29 of the '008 patent are not enabled by the specification.

We affirm the district court's holdings in all respects, except that we reverse the court's ruling that claims 1 and 3 of the '195 patent are enabled. We also vacate that part of the district court's judgment relating to infringement of those claims.

BACKGROUND[1]

Erythropoietin (EPO) is a protein consisting of 165 amino acids which stimulates the production of red blood cells. It is therefore a useful therapeutic agent in the treatment of anemias or blood disorders characterized by low or defective bone marrow production of red blood cells.

The preparation of EPO products generally has been accomplished through the concentration and purification of urine from both healthy individuals and those exhibiting high EPO levels. A new technique for producing EPO is recombinant DNA technology in which EPO is produced from cell cultures into which genetically-engineered vectors containing the EPO gene have been introduced. The production of EPO by recombinant technology involves expressing an EPO gene through the same processes that occur in a natural cell.

THE PATENTS

On June 30, 1987, the United States Patent and Trademark Office (PTO) issued to Dr. Rodney Hewick U.S. Patent 4,677,195, entitled "Method for the Purification of Erythropoietin and Erythropoietin Compositions" (the '195 patent). The patent claims both homogeneous EPO and compositions thereof and a method for purifying human EPO using reverse phase high performance liquid chromatography. The method claims are not before us. The relevant claims of the '195 patent are:

1. Homogeneous erythropoietin characterized by a molecular weight of about 34,000 daltons on SDS PAGE, movement as a single peak on reverse phase high performance liquid chromatography and a specific activity of at least 160,000 IU per absorbance unit at 280 nanometers.

* * *

3. A pharmaceutical composition for the treatment of anemia comprising a therapeutically effective amount of the homogeneous erythropoietin of claim 1 in a pharmaceutically acceptable vehicle.

4. Homogeneous erythropoietin characterized by a molecular weight of about 34,000 daltons on SDS PAGE, movement as a single peak on reverse phase high performance liquid chromatography and a specific activity of at least about 160,000 IU per absorbance unit at 280 nanometers.

* * *

6. A pharmaceutical composition for the treatment of anemia comprising a therapeutically effective amount of the homogeneous erythropoietin of claim 4 in a pharmaceutically acceptable vehicle.

Dr. Hewick assigned the patent to GI.

The other patent in this litigation is U.S. Patent 4,703,008, entitled "DNA Sequences Encoding Erythropoietin" (the '008 patent), issued on October 27, 1987, to Dr. Fu-Kuen Lin, an employee of Amgen. The claims of the '008 patent cover purified and isolated DNA sequences encoding erythropoietin and host cells transformed or transfected with a DNA sequence. The relevant claims are as follows:

2. A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding human erythropoietin.

* * *

4. A procaryotic or eucaryotic host cell transformed or transfected with a DNA sequence according to claim 1, 2 or 3 in a manner allowing the host cell to express erythropoietin.

* * *

6. A procaryotic or eucaryotic host cell stably transformed or transfected with a DNA vector according to claim 5.

7. A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding a polypeptide having an amino acid sequence sufficiently duplicative of that of erythropoietin to allow possession of the biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells, and to increase hemoglobin synthesis or iron uptake.

8. A cDNA sequence according to claim 7.

* * *

23. A procaryotic or eucaryotic host cell transformed or transfected with a DNA sequence according to claim 7, 8, or 11 in a manner allowing the host cell to express said polypeptide.

24. A transformed or transfected host cell according to claim 23 which host cell is capable of glycosylating said polypeptide.

25. A transformed or transfected mammalian host cell according to claim 24.

26. A transformed or transfected COS cell according to claim 25.

27. A transformed or transfected CHO cell according to claim 25.

* * *

29. A procaryotic host cell stably transformed or transfected with a DNA vector according to claim 28.

PROCEDURAL HISTORY

On October 27, 1987, the same day that the '008 patent was issued, Amgen filed suit against Chugai and GI. It alleged that GI infringed the '008 patent by the production of recombinant EPO (rEPO) and by use of transformed mammalian host cells containing vectors with DNA coding for the production of human EPO, and that Chugai, as a result of a collaborative relationship with GI, had induced and/or contributed to the direct infringement of the '008 patent by GI. Amgen further sought a declaration that GI's '195 patent is invalid under 35 U.S.C. §§102, 103, and 112, or, in the alternative, that Amgen does not infringe the claims of the '195 patent, and a declaration that GI and Chugai's future activities in the production and sale of rEPO will infringe the '008 patent.[2]

GI and Chugai answered and counterclaimed, asserting several affirmative defenses, including invalidity under 35 U.S.C. §§101, 102, 103, and 112; non-infringement; failure to make deposits at a public depository of biological materials allegedly necessary for enabling the best mode of practicing the invention; and unenforceability of the

[1] The district court, in a detailed opinion, fully sets out the scientific and historical background relating to the patents at issue. *See Amgen*, 13 USPQ2d at 1741–58. Familiarity with that opinion is presumed.

[2] Amgen subsequently filed a complaint with the United States International Trade Commission alleging that Chugai's importation of rEPO, manufactured in Japan using genetically engineered host cells, violated Section 337 of the Tariff Act of 1930 (19 U.S.C. §§1337, 1337a). The Commission entered an order terminating the investigation for lack of subject matter jurisdiction. This court vacated and remanded, holding that the Commission should have treated the complaint on the merits and not on jurisdictional grounds, and that the claims of Amgen's patent did not cover a process for producing rEPO. *Amgen, Inc. v. United States Int'l Trade Comm'n*, 902 F.2d 1532, 14 USPQ2d 1734 (Fed. Cir. 1990).

patent because of Amgen's alleged inequitable conduct before the PTO. GI also counterclaimed, alleging that Amgen infringed the '195 patent, asserting unfair competition, and seeking a declaratory judgment that the '008 patent was invalid and not infringed.

GI and Chugai then filed a joint motion for a partial summary judgment that Amgen infringed the claims of the '195 patent. Chugai also filed its own motion for summary judgment. On February 24, 1988, the district court granted GI's and Chugai's motion for partial summary judgment and, on January 31, 1989, the court granted Chugai's motion for partial summary judgment only to the extent of ruling that the '008 patent does not contain a process claim, an issue that is not now before us.

In response to Amgen's motion for a preliminary injunction, the district court, on February 7, 1989, issued an order finding that "Amgen had shown a reasonable likelihood of success on the merits of the validity of its patent; that it would suffer irreparable injury due to the needs of an incipient market and the attendant burdens on a new company; . . ." and that, as to the public interest, "recombinant EPO is an extraordinarily valuable medicine that promises marked relief from renal failure." Because of this public interest finding, the court determined that it would not enter an order to delay or prevent production or shipping of EPO, but would require the defendant GI to place with the court all profits from the sale of EPO.

In order to expedite trial, the parties consented to trial before a magistrate. The judge entered judgment upon findings of fact and conclusions of law set forth by the magistrate. With respect to Amgen's '008 patent, the court held that claims 2, 4, and 6 are valid, enforceable and have been infringed by GI; that infringement was not willful; that claims 7, 8, 23–27, and 29 are invalid for lack of enablement under 35 U.S.C. §112 but, if valid, were infringed by GI; that the '008 patent does not contain a process claim; and that Chugai has not infringed, contributorily infringed, or induced infringement of any claim of the '008 patent. The court also dismissed Amgen's complaint against Chugai.

With respect to GI's '195 patent, the court concluded that claims 1 and 3 are valid, enforceable, and have been infringed by Amgen; that Amgen has not infringed claims 2 and 5; that Amgen's infringement was not willful; and that claims 4 and 6 are invalid for indefiniteness under 35 U.S.C. §112, but, if valid, were infringed by Amgen. The court also concluded that Amgen did not misuse the '008 patent and that this was not an "exceptional" case under 35 U.S.C. §285.

DISCUSSION

I. AMGEN's '008 PATENT (Lin)

A. *Alleged prior invention under 35 U.S.C. §102(g)*

The first issue we review is whether the district court erred in finding that the claims directed to a purified and isolated DNA sequence encoding human EPO were not invalidated by the work of GI's Dr. Fritsch. Section 102(g) provides in relevant part that:

> A person is entitled to a patent unless—
> (g) before the applicant's invention thereof the invention was made . . . by another who had not abandoned, suppressed, or concealed it. In determining priority of invention there shall be considered not only the respective dates of conception and reduction to practice of the invention, but also the reasonable diligence of one who was first to conceive and last to reduce to practice, from a time prior to conception by the other.

Defendants assert error in the district court's legal conclusion that in this case Lin's conception occurred simultaneously with reduction to practice. *See e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1376, 231 USPQ 81, 87 (Fed. Cir. 1988), *cert. denied*, 480 U.S. 947 (1987). They claim that Fritsch was first to conceive a probing strategy of using two sets of fully-degenerate cDNA probes of two different regions of the EPO gene to screen a gDNA library, which was the strategy which the district court found eventually resulted in the successful identification and isolation of the EPO gene. Defendants further claim that Fritsch conceived this strategy in 1981, was diligent until he reduced the invention to practice in May of 1984, and thus should be held to be a 102(g) prior inventor over Lin, who reduced the invention to practice in September of 1983.

Conception is the "formation in the mind of the inventor, of a definite and permanent idea of the complete and operative invention, as it is hereafter to be applied in practice." *Hybritech*, 802 F.2d at 1376, 231 USPQ at 87 (citing 1 *Robinson on Patents* 532 (1890)); *Coleman v. Dines*, 754 F.2d 353, 359, 224 USPQ 857, 862 (Fed. Cir. 1985) (citing *Gunter v. Stream*, 573 F.2d 77, 80, 197 USPQ 482, 484 (CCPA 1978)). Conception requires both the idea of the invention's structure and possession of an operative method of making it. *Oka v. Youssefyeh*, 849 F.2d 581, 583, 7 USPQ2d 1169, 1171 (Fed. Cir. 1988).

In some instances, an inventor is unable to establish a conception until he has reduced the invention to practice through a successful experiment. This situation results in a simultaneous conception and reduction to practice. *See* 3 D. Chisum, *Patents* §10.04[5] (1990). We agree with the district court that that is what occurred in this case.

The invention recited in claim 2 is a "purified and isolated DNA sequence" encoding human EPO. The structure of this DNA sequence was unknown until 1983, when the gene was cloned by Lin; Fritsch was unaware of it until 1984. As Dr. Sadler, an expert for GI, testified in his deposition: "You have to clone it first to get the sequence." In order to design a set of degenerate probes, one of which will hybridize with a particular gene, the amino acid sequence, or a portion thereof, of the protein of interest must be known. Prior to 1983, the amino acid sequence for EPO was uncertain, and in some positions the sequence envisioned was incorrect. Thus, until Fritsch had a complete mental conception of a purified and isolated DNA sequence encoding EPO and a method for its preparation, in which the precise identity of the sequence is envisioned, or in terms of other characteristics sufficient to distinguish it from other genes, all he had was an objective to make an invention which he could not then adequately describe or define.

[1] A gene is a chemical compound, albeit a complex one, and it is well established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials, and to describe how to obtain it. *See Oka*, 849 F.2d at 583, 7 USPQ2d at 1171. Conception does not occur unless one has a mental picture of the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by its principal biological property, *e.g.*, encoding human erythropoietin, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property. We hold that when an inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, *i.e.*, until after the gene has been isolated.

Fritsch had a goal of obtaining the isolated EPO gene, whatever its identity, and even had an idea of a possible method of obtaining it, but he did not conceive a purified and isolated DNA sequence encoding EPO and a viable method for obtaining it until after Lin. It is important to recognize that neither Fritsch nor Lin invented EPO or the EPO gene. The subject matter of claim 2 was the novel *purified and isolated* sequence which codes for EPO, and neither Fritsch nor Lin knew the structure or physical characteristics of it and had a viable method of obtaining that subject matter until it was actually obtained and characterized.

[2] Defendants further argue that because the trial court found that the probing and screening method employed by Lin is what distinguished the invention of the '008 patent over the prior art, Fritsch's strategy in 1981 had priority over Lin's use of that strategy. We disagree. The trial court found that Fritsch's alleged conception in 1981 of an approach that might result in cloning the gene was mere speculation. Conception of a generalized approach for screening a DNA library that might be used to identify and clone the EPO gene of then unknown constitution is not conception of a "purified and isolated DNA sequence" encoding human EPO. It is not "a definite and permanent idea of the complete and operative invention." Fritsch's conception of a process had to be sufficiently specific that one skilled in the relevant art would succeed in cloning the EPO gene. *See Coleman*, 754 F.2d at 359, 224 USPQ at 862. Clearly, he did not have that conception because he did not know the structure of EPO or the EPO gene.

The record indicates that several companies, as well as Amgen and GI, were unsuccessful using Fritsch's approach. As the trial court correctly summarized:

> Given the utter lack of experience in probing genomic libraries with fully degenerate probes and the crudeness of the techniques available in 1981, it would have been mere speculation or at most a probable deduction from facts then known by Dr. Fritsch that his generalized approach would result in cloning the EPO gene.

13 USPQ2d at 1760. As expert testimony from both sides indicated, success in cloning the EPO gene was not assured until the gene was in fact isolated and its sequence known. Based on the uncertainties of the method and lack of information concerning the amino acid sequence of the EPO protein, the trial court was correct in concluding that neither party had an adequate conception of the DNA sequence until reduction to practice

had been achieved, Lin was first to accomplish that goal.

Defendants also argue that the court failed to consider that 1983, just prior to Lin's conception, was the relevant time for determining the completeness of Fritsch's conception, not 1981. However, the record shows that the court did consider what occurred in 1983. Moreover, Fritsch had no more of a conception in 1983 than he did in 1981, because he did not then know the sequence of the gene encoding EPO.

B. *Alleged obviousness of the inventions of claims 2, 4, and 6*

Claim 2, as noted above, recites a purified and isolated DNA sequence, and claims 4 and 6 are directed to host cells transformed with such a DNA sequence. The district court determined that claims 2, 4, and 6 are not invalid under 35 U.S.C. §103, concluding that the unique probing and screening method employed by Lin in isolating the EPO gene and the extensive effort required to employ that method made the invention nonobvious over the prior art.[1]

Obviousness under Section 103 is a question of law. *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1568, 1 USPQ2d 1593, 1597 (Fed. Cir.), *cert. denied*, 481 U.S. 1052 (1987). The district court stated that one must inquire whether the prior art would have suggested to one of ordinary skill in the art that Lin's probing and screening method should be carried out and would have a reasonable expectation of success, viewed in light of the prior art. *See In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). "Both the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure." *Id.*

[3] The district court specifically found that, as of 1983, none of the prior art references "suggest[s] that the probing strategy of using two fully-redundant [sic] sets of probes, of relatively high degeneracy [sic], to screen a human genomic library would be likely to succeed in pulling out the gene of interest." 13 USPQ2d at 1768. While it found that defendants had shown that these procedures were "obvious to try," the references did not show that there was a reasonable expectation of success. *See In re O'Farrell*, 853 F.2d 894, 903–04, 7 USPQ2d 1673, 1680–81 (Fed. Cir. 1988).

Defendants challenge the district court's determination, arguing that, as of September, 1983, one of ordinary skill in the art would have had a reasonable expectation of success in screening a gDNA library by Lin's method in order to obtain EPO. We agree with the district court's conclusion, which was supported by convincing testimony. One

[1] We note that both the district court and the parties have focused on the obviousness of a process for making the EPO gene, despite the fact that it is products (genes and host cells) that are claimed in the patent, not processes. We have directed our attention accordingly, and do not consider, independently whether the products would have been obvious aside from the alleged obviousness of a method of making them.

witness, Dr. Davies of Biogen, another biotechnology company that had worked on EPO, stated that he could not say whether Biogen scientists would have succeeded in isolating the EPO gene if Biogen had the EPO fragments that were available to Lin in 1983. Dr. Wall, a professor at UCLA, testified that it would have been "difficult" to find the gene in 1983, and that there would have been no more than a fifty percent chance of success. He said, "you couldn't be certain where in the genomic DNA your probe might fall." The court found that no one had successfully screened a genomic library using fully-degenerate probes of such high redundancy as the probes used by Lin. In the face of this and other evidence on both sides of the issue, it concluded that defendants had not shown by clear and convincing evidence that the procedures used by Lin would have been obvious in September 1983. We are not persuaded that the court erred in its decision.

Defendants assert that whether or not it would have been obvious to isolate the human EPO gene from a gDNA library with fully-degenerate probes is immaterial because it was obvious to use the already known monkey EPO gene as a probe. Defendants point out that, in the early 1980s, Biogen did significant work with an EPO cDNA obtained from a baboon, and that they used it as a probe to hybridize with the corresponding gene in a human gDNA library. However, this technique did not succeed until after Lin isolated the EPO gene with his fully-degenerate set of probes.

To support its obviousness assertion, defendants rely upon the testimony of their expert, Dr. Flavell, who testified that the overall homology of baboon DNA and human DNA was "roughly 90 percent". While this testimony indicates that it might have been feasible, perhaps obvious to try, to successfully probe a human gDNA library with a monkey cDNA probe, it does not indicate that the gene could have been identified and isolated with a reasonable likelihood of success. Neither the DNA nucleotide sequence of the human EPO gene nor its exact degree of homology with the monkey EPO gene was known at the time.

Indeed, the district court found that Lin was unsuccessful at probing a human gDNA library with monkey cDNA until after he had isolated the EPO gene by using the fully-degenerate probes. Based on the evidence in the record, the district court found there was no reasonable expectation of success in obtaining the EPO gene by the method that Lin eventually used. While the idea of using the monkey gene to probe for a homologous human gene may have been obvious to try, the realization of that idea would not have been obvious. There were many pitfalls. Hindsight is not a justifiable basis on which to find that ultimate achievement of a long sought and difficult scientific goal was obvious. The district court thoroughly examined the evidence and the testimony. We see no error in its result. Moreover, if the DNA sequence was not obvious, host cells containing such sequence, as claimed in claims 4 and 6, could not have been obvious. We conclude that the district court did not err in holding that the claims of the patent are not invalid under Section 103.

C. *Best Mode*

Defendants argue that the district court erred in failing to hold the '008 patent invalid under 35 U.S.C. §112, asserting that Lin failed to disclose the best mammalian host cells known to him as of November 30, 1984, the date he filed his fourth patent application.

The district court found that the "best mode" of practicing the claimed invention was by use of a specific genetically-heterogeneous strain of Chinese hamster ovary (CHO) cells, which produced EPO at a rate greater than that of other cells. It further found that this strain was disclosed in Example 10 and that Lin knew of no better mode. GI argues that Lin's best mode was not adequately disclosed in Example 10 because one skilled in the art could not duplicate Lin's best mode without his having first deposited a sample of the specific cells in a public depository. The issue before us therefore is whether the district court erred in concluding that Example 10 of the '008 patent satisfied the best mode requirement as to the invention of the challenged claims and that a deposit of the preferred CHO cells was not necessary.

[4] A determination whether the best mode requirement is satisfied is a question of fact, *DeGeorge v. Bernier*, 768 F.2d 1318, 1324, 226 USPQ 758, 763 (Fed. Cir. 1985); we

[1] At this point, some explanation of the involved technology may be useful, consistent with that expressed in the district court opinion. DNA consists of two complimentary strands of nucleotides, which include the four basic compounds adenine(A), guanine(G), cytosine(C), and thymine(T), oriented so that bases from one strand weakly bond to the bases of the opposite strand. A bonds with T, and G bonds with C to form complementary base pairs. This bonding process is called hybridization and results in the formation of a stable duplex molecule. The structure also includes 5-carbon sugar moieties with phosphate groups.

The genetic code for a particular protein depends upon sequential groupings of three nucleotides, called codons. Each codon codes for a particular amino acid. Since there are four nucleotide bases and three bases per codon, there are 64 (4x4x4) possible codons. Because there are only 20 natural amino acids, most amino acids are specified by more than one codon. This is referred to as a "redundancy," or "degeneracy" in the genetic code, a fact that complicates and renders more difficult the techniques of recombinant DNA.

In order to prepare a protein using recombinant DNA technology, the gene for the protein must first be isolated from a cell's total DNA by screening a library of that cell's DNA. The DNA library is screened by use of a probe, a synthetic radiolabelled nucleic acid sequence which can be used to detect and isolate complementary base sequences by hybridization. To design a probe when the gene has not yet been isolated, a scientist must know the amino acid sequence, or a portion thereof, of the protein of interest. Because some amino acids have several possible codons and the researcher cannot know which of the possible codons will actually code for an amino acid, he or she may decide to design a set of probes that covers all possible codons for each amino acid comprising the protein, known as a "fully-degenerate" set of probes. A library to be screened can be a genomic library (gDNA), which contains a set of all the DNA sequences found in an organism's cells or a complementary DNA (cDNA) library, which is much smaller and less complex than a gDNA library, and is used frequently when the tissue source for a given gene is known.

[1] Defendants assert that all the claims should be invalid for failure to disclose the best mode. We perceive that the best mode issue only relates to the host cell claims, 4, 6, 23–27, and 29. Absent inequitable conduct, a best mode defense only affects those claims covering subject matter the practice of which has not been disclosed in compliance with the best mode requirement. *See Northern Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 940, 15 USPQ2d 1321, 1328 (Fed. Cir.), *cert. denied*, ____ U.S. ____, 111 S.Ct. 296 (1990).

therefore review the district court's finding under a clearly erroneous standard.

35 U.S.C. §112 provides in relevant part:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, *and shall set forth the best mode contemplated by the inventor of carrying out his invention.* (Emphasis added).

This court has recently discussed the best mode requirement, pointing out that its analysis has two components. *Chemcast Corp. v. Arco Indus. Corp.*, 913 F.2d 923, 927, 16 USPQ2d 1033, 1036 (Fed. Cir. 1990). The first is a subjective one, asking whether, at the time the inventor filed his patent application, he contemplated a best mode of practicing his invention. If he did, the second inquiry is whether his disclosure is adequate to enable one skilled in the art to practice the best mode or, in other words, whether the best mode has been concealed from the public. The best mode requirement thus is intended to ensure that a patent applicant plays "fair and square" with the patent system. It is a requirement that the *quid pro quo* of the patent grant be satisfied. One must not receive the right to exclude others unless at the time of filing he has provided an adequate disclosure of the best mode known to him of carrying out his invention. Our case law has interpreted the best mode requirement to mean that there must be no concealment of a mode known by the inventor to be better than that which is disclosed. *Hybritech Inc. v. Monoclonal Antibodies, Inc.* 802 F.2d 1367, 1384-85, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987). Section 282 imposes on those attempting to prove invalidity the burden of proof. We agree that the district court did not err in finding that defendants have not met their burden of proving a best mode violation.

As noted above, the district court found that the best mode of making the CHO cells was set forth in Example 10. As the district court stated, while it was not clear which of two possible strains Lin considered to be the best, the cell strain subjected to 1000 nanomolar MTX (methotrexate) or that subjected to 100 nanomolar MTX, the best mode was disclosed because both were disclosed.[4]

Defendants argue that this disclosure is not enough, that a deposit of the cells was required.

Defendants contend that "[i]n the field of living materials such as microorganisms and cell cultures," we should require a biological deposit so that the public has access to exactly the best mode contemplated by the inventor. This presents us with a question of first impression concerning the best mode requirement for patents involving novel genetically-engineered biological subject matter.

For many years, it has been customary for patent applicants to place microorganism samples in a public depository when such a sample is necessary to carry out a claimed invention. This practice arose out of the development of antibiotics, when microorganisms obtained from soil samples uniquely synthesized antibiotics which could not be readily prepared chemically or otherwise. *In re Argoudelis*, 434 F.2d 1390, 168 USPQ 99 (CCPA 1970). Such a deposit has been considered adequate to satisfy the *enablement* requirement of 35 U.S.C. §112, when a written description alone would not place the invention in the hands of the public and physical possession of a unique biological material is required. *See, e.g., In re Wands*, 858 F.2d 731, 735-36, 8 USPQ2d 1400, 1403 (Fed. Cir. 1988) ("Where an invention depends on the use of living materials . . . it may be impossible to enable the public to make the invention (*i.e.*, to obtain these living materials) solely by means of written disclosure."); *In re Lundak*, 773 F.2d 1216, 1220, 227 USPQ 90, 93 (Fed. Cir. 1985) ("When an invention relates to a new biological material, the material may not be reproducible even when detailed procedures and a complete taxonomic description are included in the specification."); *see generally* Hampar, *Patenting of Recombinant DNA Technology: The Deposit Requirement*, 67 J. Pat. & Trademark Off. Soc'y 569, 607 (1985) ("The deposit requirement is a non-statutory mechanism for ensuring compliance with the 'enabling' provision under 35 U.S.C. §112.").

The district court found that the claims at issue require the use of biological materials that were capable of being prepared in the laboratory from readily available biological cells, using the description in Example 10. The court also found that there were no starting materials that were not publicly available, that were not described, or that required undue experimentation for their preparation in order to carry out the best mode. The court noted that Lin testified that the isolation of the preferred strain was a "routine limited dilution cloning procedure[.]" well known in the art. Dr. Simonsen, GI's own expert, testified that the disclosed procedures were "standard" and that:

> with the vectors and the sequences shown in Example 10, I have no doubt that someone eventually could reproduce—well, could generate cell lines [sic, strains] making some level of EPO, and they could be better, they could be worse in terms of EPO production.

The district court relied on this testimony, and, upon review, we agree with its determination. The testimony accurately reflects that the invention, as it relates to the *best mode* host cells, could be practiced by one skilled in the art following Example 10. Thus, the best mode was disclosed and it was adequately enabled.

[5] These materials are therefore not analogous to the biological cells obtained from unique soil samples. When a biological sample required for the practice of an invention is obtained from nature, the invention may be incapable of being practiced without access to that organism. Hence the deposit is required in that case. On the other hand, when, as is the case here, the organism is created by insertion of genetic material into a cell obtained from generally available sources, then all that is required is a description of the best mode and an adequate description of the means of carrying out the invention, not deposit of the cells. If the cells can be prepared without undue experimentation from known materials, based on the description in the patent specification, a deposit is not required. *See Feldman v. Aunstrup*, 517 F.2d 1351, 1354, 186 USPQ 108, 111 (CCPA 1975), ("No problem exists when the microorganisms used are known and readily available to the public."), *cert. denied*, 424 U.S. 912 [188 USPQ 720] (1976). Since the court found that that is the case here, we therefore hold that there is no failure to comply with the best mode requirement for lack of a deposit of the CHO cells, when the *best mode* of preparing the cells has been disclosed and the best mode cells have been enabled, *i.e.*, they can be prepared by one skilled in the art from known materials using the description in the specification.

Defendants also contend that the examiner's rejection of the application that matured into the '008 patent for failure to make a publicly accessible biological deposit supports its argument. U.S. Patent Application Serial No. 675,298, Prosecution History at 179 (First Rejection July 3, 1986). However, that rejection was withdrawn after an oral interview and a written argument that the invention did not require a deposit. *Id.* at 208.

We also note that the PTO has recently prescribed guidelines concerning the deposit of biological materials. *See* 37 C.F.R. §1.802(b) (1990) (biological material need not be deposited "if it is known and readily available to the public or can be made or isolated without undue experimentation"). The PTO, in response to a question as to whether the deposit requirement is applicable to the best mode requirement, as distinct from enablement, said:

> The best mode requirement is a safeguard against the possible selfish desire on the part of some people to obtain patent protection without making a full disclosure. The requirement does not permit an inventor to disclose only what is known to be the second-best embodiment, retaining the best. The fundamental issue that should be addressed is whether there was evidence to show the quality of an applicant's best mode disclosure is so poor as to effectively result in concealment. *In re Sherwood*, 615 F.2d 809, 204 USPQ 537 (CCPA 1980). If a deposit is the only way to comply with the best mode requirement then the deposit must be made.

52 *Fed.Reg.* 34080, 34086 (Sept. 8, 1987).[5]

We see no inconsistency between the district court's decision, which we affirm here, and these guidelines.

[6] Defendants also assert that the record shows that scientists were unable to duplicate Lin's genetically-heterogeneous best mode cell strain. However, we have long held that the issue is whether the disclosure is "adequate," not that an exact duplication is necessary. Indeed, the district court stated that

> [t]he testimony is clear that no scientist could ever duplicate exactly the best mode used by Amgen, but that those of ordinary skill in the art could produce mammalian

[4] In its opinion, the district court stated that "the best way to express EPO was from mammalian cells . . . and that a cell line derived from 11 possible clones from the CHO B11, 3, 1 cell strain was to be used for Amgen's master working cell bank, which was expected to be started on November 26, 1984." 13 USPQ2d at 1772. At another point, the court stated that Amgen "did disclose the best mode in Example 10 of the invention, when it described the production rates of the 100 nanomolar-amplified cells (the B11 3,1 cell strain) and one micromolar-treated cells." *Id.*

[5] *See also* 53 *Fed. Reg.* 39420, 39425 (Oct. 6, 1989) (comment re "deposit [to] satisfy the best mode requirement"); 52 *Fed. Reg.* 34080, 34080 and 34084 (Sept. 8, 1987). (deposit may be required to satisfy enablement, best mode, or distinct claim requirements of §112).

host cell strains or lines with similar levels of production identified in Example 10." 13 USPQ2d at 1774. What is required is an adequate disclosure of the best mode, not a guarantee that every aspect of the specification be precisely and universally reproducible. *See In re Gay*, 309 F.2d 769, 773, 135 USPQ 311, 316 (CCPA 1962).

Defendants finally argue that Lin's failure to deposit the transfected cells notwithstanding the fact that he was willing to deposit essentially worthless cell material was evidence of deliberate concealment. We have already stated that deposit of the host cells containing the rEPO gene was not necessary to satisfy the best mode requirement of Section 112. The best mode was disclosed and a deposit was not necessary to carry it out. Therefore, the fact that some cells were deposited, but not others, is irrelevant.

D. *Enablement of claims 7, 8, 23-27, and 29*

Amgen argues that the district court's holding that GI "provided clear and convincing evidence that the patent specification is insufficient to enable one of ordinary skill in the art to make and use the invention claimed in claim 7 of the '008 patent without undue experimentation" constituted legal error. 13 USPQ2d at 1776. Amgen specifically argues that the district court erred because it "did not properly address the factors which this court has held must be considered in determining lack of enablement based on assertion of undue experimentation," citing this court's decision in *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404.

Claim 7 is a generic claim, covering all possible DNA sequences that will encode any polypeptide having an amino acid sequence "sufficiently duplicative" of EPO to possess the property of increasing production of red blood cells. As claims 8, 23-27, and 29, dependent on claim 7, are not separately argued, and are of similar scope, they stand or fall with claim 7. *See In re Dillon*, 919 F.2d 688, 692, 16 USPQ2d 1897, 1900 (Fed. Cir. 1990) (in banc).

[7] Whether a claimed invention is enabled under 35 U.S.C. §112 is a question of law, which we review *de novo*. *Moleculon Research Corp. v. CBS, Inc.*, 793 F.2d 1261, 1268, 229 USPQ 805, 811 (Fed. Cir. 1986), *cert. denied*, 479 U.S. 1030 (1987). "To be enabling under §112, a patent must contain a description that enables one skilled in the art to make and use the claimed invention." *Atlas Powder Co. v. E.I. duPont De Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984).

That some experimentation is necessary does not constitute a lack of enablement; the amount of experimentation, however, must not be unduly extensive. *Id.* The essential question here is whether the scope of enablement of claim 7 is as broad as the scope of the claim. *See generally In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970); 2 D. Chisum, *Patents* §7.03[7][b] (1990).

The specification of the '008 patent provides that:

> one may readily design and manufacture genes coding for microbial expression of polypeptides having primary conformations which differ from that herein specified for mature EPO in terms of the identity or location of one or more residues (e.g., substitutions, terminal and intermediate additions and deletions).
>
> * * *
>
> DNA sequences provided by the present invention are thus seen to comprehend all DNA sequences suitable for use in securing expression in a procaryotic or eucaryotic host cell of a polypeptide product having at least a part of the primary structural conformation and one or more of the biological properties of erythropoietin, and selected from among: (a) the DNA sequences set out in FIGS. 5 and 6; (b) DNA sequences which hybridize to the DNA sequences defined in (a) or fragments thereof; and (c) DNA sequences which, but for the degeneracy of the genetic code, would hybridize to the DNA sequences defined in (a) and (b).

The district court found that over 3,600 different EPO analogs can be made by substituting at only a single amino acid position, and over a million different analogs can be made by substituting three amino acids. The patent indicates that it embraces means for preparation of "numerous" polypeptide analogs of EPO. Thus, the number of claimed DNA encoding sequences that can produce an EPO-like product is potentially enormous.

In a deposition, Dr. Elliott, who was head of Amgen's EPO analog program, testified that he did not know whether the fifty to eighty EPO analogs Amgen had made "had the biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells, and to increase hemoglobin synthesis or iron uptake." Based on this evidence, the trial court concluded that "defendants had provided clear and convincing evidence that the patent specification is insufficient to enable one of ordinary skill in the art to make and use the invention claimed in claim 7 of the '008 patent without undue experimentation." 13 USPQ at 1776. In making this determination, the court relied in particular on the lack of predictability in the art, as demonstrated by the testimony of both Dr. Goldwasser, another scientist who worked on procedures for purifying urinary EPO (uEPO), and Dr. Elliott. After five years of experimentation, the court noted, "Amgen is still unable to specify which analogs have the biological properties set forth in claim 7." *Id.*

We believe the trial court arrived at the correct decision, although for the wrong reason. By focusing on the biological properties of the EPO analogs, it failed to consider the enablement of the DNA sequence analogs, which are the subject of claim 7. Moreover, it is not necessary that a patent applicant test all the embodiments of his invention. *In re Angstadt*, 537 F.2d 498, 502, 190 USPQ 214, 218 (CCPA 1976); what is necessary is that he provide a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of his claims. For DNA sequences, that means disclosing how to make and use enough sequences to justify grant of the claims sought. Amgen has not done that here. In addition, it is not necessary that a court review all the *Wands* factors to find a disclosure enabling. They are illustrative, not mandatory. What is relevant depends on the facts, and the facts here are that Amgen has not enabled preparation of DNA sequences sufficient to support its all-encompassing claims.

[8] It is well established that a patent applicant is entitled to claim his invention generically, when he describes it sufficiently to meet the requirements of Section 112. *See Utter v. Hiraga*, 845 F.2d 993, 998, 6 USPQ2d 1709, 1714 (Fed. Cir. 1988) ("A specification may, within the meaning of 35 U.S.C. §112 ¶1, contain a written description of a broadly claimed invention without describing all species that claim encompasses."). *In re Robins*, 429 F.2d 452, 456-57, 166 USPQ 552, 555 (CCPA 1970) ("[R]epresentative samples are not required by the statute and are not an end in themselves."). Here, however, despite extensive statements in the specification concerning all the analogs of the EPO gene that can be made, there is little enabling disclosure of particular analogs and how to make them. Details for preparing only a few EPO analog genes are disclosed. Amgen argues that this is sufficient to support its claims; we disagree. This "disclosure" might well justify a generic claim encompassing these and similar analogs, but it represents inadequate support for Amgen's desire to claim all EPO gene analogs. There may be many other genetic sequences that code for EPO-type products. Amgen has told how to make and use only a few of them and is therefore not entitled to claim all of them.

In affirming the district court's invalidation of claims 7, 8, 23-27, and 29 under Section 112, we do not intend to imply that generic claims to genetic sequences cannot be valid where they are of a scope appropriate to the invention disclosed by an applicant. That is not the case here, where Amgen has claimed every possible analog of a gene containing about 4,000 nucleotides, with a disclosure only of how to make EPO and a very few analogs.

The district court properly relied upon *Fisher*[*] in making its decision. In that case, an applicant was attempting to claim an adrenocorticotrophic hormone preparation containing a polypeptide having at least twenty-four amino acids of a specified sequence. Only a thirty-nine amino acid product was disclosed. The court found that applicant could not obtain claims that are insufficiently supported and hence not in compliance with the first paragraph of 35 U.S.C. §112. It stated:

> Appellant's parent application, therefore, discloses no products, inherently or expressly, containing other than 39 amino acids, yet the claim includes all polypeptides, of the recited potency and purity, having at least 24 amino acids in the chain in the recited sequence. The parent specification does not enable one skilled in the art to make or obtain ACTHs with other than 39 amino acids in the chain, and there has been no showing that one of ordinary skill would have known how to make or obtain such other ACTHs without undue experimentation. As for appellant's conclusion that the 25th to 39th acids in the chain are unnecessary, it is one thing to make such a statement when persons skilled in the art are able to make or obtain ACTH having other than 39 amino acids, it is quite another thing when they are not able to do so. In the latter situation, the statement is in no way "enabling" and hence lends no further support for the broad claim. We conclude that appellant's parent applica-

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[*] *Cf. Hormone Research Foundation, Inc. v. Genentech, Inc.*, 904 F.2d 1558, 15 USPQ2d 1039 (Fed. Cir. 1990). In *Hormone Research*, this court, in a remand, directed the district court to consider the effect of *United States Steel Corp. v. Phillips Petroleum Co.*, 865 F.2d 1247, 8 USPQ2d 1461 (Fed. Cir. 1989) and *In re Hogan*, 559 F.2d 595, 194 USPQ 527 (CCPA 1977) on *Fisher* in its enablement analysis. The facts of our case are distinguishable from those in *Hormone Research*, *United States Steel*, and *Hogan*.

tion is insufficient to support a claim as broad as claim 4.

* * *

[Section 112] requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. *Fisher*, 427 F.2d at 836, 839, 166 USPQ at 21-22, 24.

Considering the structural complexity of the EPO gene, the manifold possibilities for change in its structure, with attendant uncertainty as to what utility will be possessed by these analogs, we consider that more is needed concerning identifying the various analogs that are within the scope of the claim, methods for making them, and structural requirements for producing compounds with EPO-like activity. It is not sufficient, having made the gene and a handful of analogs whose activity has not been clearly ascertained, to claim all possible genetic sequences that have EPO-like activity. Under the circumstances, we find no error in the court's conclusion that the generic DNA sequence claims are invalid under Section 112.

E. *Inequitable Conduct*

Defendants argue that the '008 patent claims are unenforceable as a result of an asserted misrepresentation of the number of probes Lin used for the monkey gene cloning described in Example 3 of his patent. Relying on the district court's finding that Lin had said that a "full set" mixture of 128 "EpV." probes[9] was used for monkey cDNA screening, whereas only a 16-member "subset" of the EpV mixture was actually used, defendants argue that the court ought to have found that the representations were material.

[9] The essential elements of proof of inequitable conduct include intent to deceive and materiality. After finding threshold levels of materiality and intent, the trial court must balance the two and determine, in its discretion, whether inequitable conduct has occurred. *J.P. Stevens & Co. v. Lex Tex Ltd., Inc.*, 747 F.2d 1553, 1560, 223 USPQ 1089, 1092 (Fed. Cir. 1984), *cert. denied*, 474 U.S. 822 (1985). While we review an ultimate conclusion of inequitable conduct under an abuse of discretion standard, *Kingsdown Medical Consultants, Ltd. v. Hollister Inc.*, 863 F.2d 867, 876, 9 USPQ2d 1384, 1392 (Fed. Cir. 1988) (in banc), *cert. denied*, 490 U.S. 1067 (1989), the underlying factual threshold findings are reviewed under a clearly erroneous standard.

Lin set out to clone the EPO gene by more than one method, including using degenerate human probes and monkey probes. It is not disputed that he did isolate the human EPO gene from a genomic library using two different 128-member pools of probes made from fragments of the human EPO protein. Thereafter, he also attempted to use the human sequence probes to find the monkey EPO cDNA to be used later as a probe to hybridize with the human EPO gene. Example 3 of the '008 patent describes this work, indicating that the screening yielded seven positive clones. It also reports that a subset of the human EpV mixture was used for DNA sequencing work. When Lin published his monkey cDNA cloning work in a scientific journal, he also reported the use of 128 EpV probes to screen the monkey library. Lin screened the monkey library with the full mixture of 128 EpV probes and with one of eight subsets of probes which made up the full EpV mixture. In response to a question whether a subset of EpV probes was used in the first screening of the monkey cDNA library, Lin testified:

> I don't know which we used, the subset first or used the full set first. I cannot recall exactly. It looks like the subset was first defining the number, yes.

This answer constituted the sole basis for the court's finding that, "[a]t trial, Lin admitted he only used a subset of the EpV 128 probes in screening the cDNA library." 13 USPQ2d at 1778.

We consider that the district court's finding of an "admission" of misrepresentation in Lin's testimony and its conclusion that GI "presented clear and convincing evidence of a misrepresentation" was clearly erroneous. That Lin did not recall whether he first screened the monkey cDNA library with a full set of probes or a subset of probes, and his answer that "it looks like" he used the subset, are certainly not clear admissions that he only used a subset. However, the district court was correct in concluding that, even if there had been an erroneous statement, it was not material because Lin succeeded in cloning the EPO gene first with his use of the fully-degenerate probes. Thus, his testimony does not provide clear and convincing evidence that he misrepresented to the PTO the number of probes used. He did use 128-member probes as well as a subset. Moreover, this evidence does not create an inference of an intent to mislead. The court properly concluded that there was no inequitable conduct in prosecuting the '008 patent.

[9] The probes designated "EpV." were from EPO amino acid sequence region 46-52.

II. GI's '195 PATENT (Hewick)

A. *Enablement of claims 1 and 3*

Amgen challenges the district court's determination that "the '195 patent enables a person of ordinary skill in the art to obtain homogeneous EPO [including rEPO and uEPO] from natural sources" having a mean *in vivo* specific activity of at least 160,000.[10] 13 USPQ2d at 1794. Claims 1 and 3 contain the limitation that EPO have a specific activity of at least 160,000 IU/AU. The district court found, based upon expert testimony from both sides, that to those skilled in the art, in the absence of an express statement in the patent, the claims would be construed to refer to *in vivo* rather than *in vitro* specific activity. To support its challenge, Amgen asserts that the district court's determination is contradicted by GI's own bioassay data and by the district court's finding that "the '195 patent fails to enable the purification of rEPO." Amgen also asserts that the district court erred in relying solely on an *in vitro* measure of specific activity, having initially construed the '195 claims as requiring an *in vivo* measure to avoid invalidity for indefiniteness.

35 U.S.C. §112 requires that an invention be described "in such full, clear, concise, and exact terms as to enable any person skilled in the art . . . to make and use the same." We review a determination of enablement as a question of law. *Moleculon Research Corp. v. CBS, Inc.*, 793 F.2d 1261, 1268, 229 USPQ 805, 811 (Fed. Cir. 1986), *cert. denied*, 479 U.S. 1030 (1987).

We do not consider the court's finding that the assay measurement was an *in vivo* one to be erroneous in view of the testimony it heard. That being the case, the question is whether the court erred in concluding that the claims requiring 160,000 IU/AU by an *in vivo* measurement were enabled. We conclude that it did err.

Defendants have produced no evidence that it ever prepared EPO with a specific activity of at least 160,000 IU/AU *in vivo* using the disclosed methods. In its report to the FDA, GI stated that it had purified uEPO material "to homogeneity" by subjecting partially purified uEPO material to reverse phase high performance liquid chromatography (RP-HPLC), the technique taught by Hewick in the '195 patent. The district court found that GI reported to the FDA that the specific activity of uEPO, based on *in vivo* bioassays, was only 109,000 IU/AU.[11] GI originally arrived at the figure of 160,000 IU/AU by calculation, before it had the capacity to derive quantitative information from bioassays. Hewick subjected the EPO to RP-HPLC, and obtained an actual value of 83,000 IU/AU. After weighing the chromatograph, he found that "at least fifty percent" of the area under the chromatograph curve was attributable to something other than EPO. He then doubled the 83,000, and arrived at a theoretical specific activity of "at least about 160,000 IU/AU." That procedure, while possibly valid as a means for estimating the specific activity of a pure sample, does not establish that GI had a workable method for actually obtaining the pure material that it claimed.

Moreover, the work of others shows that Hewick did not enable the preparation of uEPO having an *in vivo* specific activity of at least 160,000, as the claims required. Dr. Kawakita, a scientist at Kummamoto University in Japan, reported an *in vivo* specific activity of 101,000 IU/AU when using RP-HPLC according to Hewick's method. This is similar to the 109,000 value reported to the FDA by GI. Kawakita did report a value of 188,000, but did not follow the teachings in the '195 patent. Defendants also rely on the testimony of Fritsch that "I've also seen further data in Chugai's PLA indicating additional urinary EPO preparation that had activities of 190,000, I believe, units per absorbance unit." However, the document to which Fritsch referred was not offered into evidence by GI after Amgen objected to its introduction and is not before us.

Defendants argue that Dr. Kung's uEPO test result of 173,640 IU/AU in an *in vitro* test supports the enablement of its claims. Amgen argues that an *in vivo* test result would only have been 65 percent of the *in vitro* result and thus would not have met the 160,000 IU/AU limitation of the claims. The district court relied on Kung, despite the demonstrated disparity between the results of *in vitro* and *in vivo* testing.

[10] The potency of EPO in the '195 patent is stated as its specific activity, expressed as a ratio of International Units (which measures the ability of EPO to cause formation of red blood cells) per absorbance unit (the amount of light absorbed by a sample of EPO measured by a spectrophotometer at a given wavelength, 280 nanometers), *i.e.*, IU/AU.

[11] Defendants provided no evidence that faulty purification procedures or other missteps caused its failure to obtain 160,000 IU/AU *in vivo* material as claimed in the '195 patent.

[10] It is not absolutely clear to us that, for uEPO, the *in vivo* specific activity is 65 percent of the *in vitro* specific activity. Nonetheless, Kung's measurement, being *in vitro*, does not demonstrate enablement of the claimed invention, and that fact means that the court erred in finding enablement. Added to this fact is the difference that exists between the *in vivo* results for rEPO and uEPO [9], and the other lack of support for the 160,000 limitation. Under these circumstances, we hold that the district court erred in accepting the *in vitro* data as support for claims containing what has been found to be an *in vivo* limitation.

In addition to the question of enablement regarding uEPO, the district court found that the only purification attempt on rEPO in the manner set out in the '195 patent failed to provide homogeneous EPO. The patent itself, in Example 2, discloses GI's purification efforts on rEPO and indicates that GI did not obtain purified rEPO. As the district court found, "[t]he patent does not contain any procedures . . . for purifying rEPO to the point that RP-HPLC will be successful." 13 USPQ2d at 1758. Thus, the patent fails to enable purification of either rEPO or uEPO.[9] *See In re Rainer*, 377 F.2d 1006, 1012, 153 USPQ 802, 807 (CCPA 1967) ("specification is evidence of its own inadequacy").

The burden of showing non-enablement is Amgen's, not GI's, but in the case of a challenged patent, when substantial discovery has occurred, and there is no credible evidence that the claimed purified material can be made by those skilled in the art by the disclosed process, and all evidence from both the inventor and his assignee and from third parties is to the contrary, we conclude that Amgen has met its burden to show that the claims have not been adequately enabled. We do not hold that one must always prove that a disclosed process operates effectively to produce a claimed product. But, under these circumstances, we conclude that the court erred in holding that claims 1 and 3 were properly enabled.

B. *Indefiniteness of claims 4 and 6*

The district court held claims 4 and 6 of the '195 patent invalid because their specific activity limitation of "at least about 160,000" was indefinite. Defendants challenge this holding, asserting that there is no evidence that claims 4 and 6 do not comply with the requirements of 35 U.S.C. §112.

The statute requires that "[t]he specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." A decision as to whether a claim is invalid under this provision requires a determination whether those skilled in the art would understand what is claimed. *See Shatterproof Glass Corp. v. Libbey-Owens Ford Co.*, 758 F.2d 613, 624, 225 USPQ 634, 641 (Fed. Cir. 1985) (Claims must "reasonably apprise those skilled in the art" as to their scope and be "as precise as the subject matter permits."). The district court found that "bioassays provide an imprecise form of measurement with a range of error" and that use of the term "about" 160,000 IU/AU, coupled with the range of error already inherent in the specific activity limitation, served neither to distinguish the invention over the close prior art (which described preparations of 120,000 IU/AU), nor to permit one to know what specific activity values below 160,000, if any, might constitute infringement. 13 USPQ2d at 1787. It found evidence of ambiguity in the fact that Chugai, GI's partner, itself questioned whether the specific activity value of 138,000 IU/AU for its own rEPO was within the claim coverage.

In prosecuting the '195 patent, GI disclosed to the examiner a publication by Miyake et al., which discloses a uEPO product having an *in vivo* specific activity of 128,620 IU/AU. When the examiner noticed this disclosure late in the prosecution, he rejected the '195 claims with a specific activity limitation of "at least 120,000" as anticipated by the Miyake et al. disclosure. It was only after the "at least 120,000" claims were cancelled that GI submitted the "at least about 160,000" claim language.

The court found the "addition of the word 'about' seems to constitute an effort to recapture . . . a mean activity somewhere between 120,000, which the patent examiner found was anticipated by the prior art, and [the] 160,000 IU/AU" claims which were previously allowed. Because "the term 'about' 160,000 gives no hint as to which mean value between the Miyake et al. value of 128,620 and the mean specific activity level of 160,000 constitutes infringement," the court held the "at least about" claims to be invalid for indefiniteness. 13 USPQ2d at 1787-88. This holding was further supported by the fact that nothing in the specification, prosecution history, or prior art provides any

[9] The court quoted Chugai to the effect that the *in vivo* activity of uEPO is 65 percent that of rEPO.

[9] Chugai's sample reported to the Food and Drug Administration was not purified by the disclosed process.

indication as to what range of specific activity is covered by the term "about," and by the fact that no expert testified as to a definite meaning for the term in the context of the prior art. In his testimony, Fritsch tried to define "about" 160,000, but he could only say that while "somewhere between 155[,000] might fit within that number," he had not "given a lot of direct considerations to that. . . ."

[11] When the meaning of claims is in doubt, especially when, as is the case here, there is close prior art, they are properly declared invalid. *Standard Oil Co. v. American Cyanamid Co.*, 774 F.2d 448, 453, 227 USPQ 293, 297 (Fed. Cir. 1985). We therefore affirm the district court's determination on this issue. We also note that, in view of our reversal of the district court's holding that claims 1 and 3 are valid, it is clear that claims 4 and 6 would also be invalid without the "about" limitation. In arriving at this conclusion, we caution that our holding that the term "about" renders indefinite claims 4 and 6 should not be understood as ruling out any and all uses of this term in patent claims. It may be acceptable in appropriate fact situations, *e.g., W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1557, 220 USPQ 303, 316 (Fed. Cir. 1983) ("use of 'stretching . . . at a rate exceeding about 10% per second' in the claims is not indefinite"), even though it is not here.

C. *Inequitable Conduct*

The district court concluded that GI did not engage in inequitable conduct with respect to the '195 patent. Amgen challenges this holding, asserting, *inter alia*, that GI displayed an intent to mislead by withholding data showing *in vivo* specific activity of homogenous uEPO and withholding information on the range of error in EPO bioassays.

It is fundamental that to establish inequitable conduct, an intent to deceive is required. *RCA Corp. v. Data General Corp.*, 887 F.2d 1056, 1065, 12 USPQ2d 1449, 1456-57 (Fed. Cir. 1989). A finding of an intent to deceive may follow from an assessment of materiality, knowledge, and surrounding circumstances, including evidence of good faith. *Kingsdown Medical Consultants Ltd. v. Hollister Inc.*, 863 F.2d 867, 876, 9 USPQ2d 1384, 1392 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1067 (1989). The district court found no such intent, stating:

> the record is devoid of any evidence that would establish deliberate knowing withholdings of any kind by Dr. Hewick or GI. Dr. Hewick was a credible witness who spoke carefully and candidly about his work. There is no evidence that Dr. Hewick withheld any information he believed was material to the patent examiner.

Amgen, 13 USPQ2d at 1791. There is no clear error in this finding. Amgen raises no inequitable conduct issues that were not fully considered by the district court. We have reviewed the record and find no abuse of discretion on the part of the district court. This is also not an exceptional case.

III. OTHER ISSUES

In view of our conclusion that the district court erred as a matter of law in holding that claims 1 and 3 of the '195 patent are not invalid, we vacate the district court's holdings relating to infringement of those claims. We have considered the other arguments by counsel on both sides and find them to be without merit.

CONCLUSION

We conclude that the district court did not err in its findings that claims 2, 4, and 6 of the '008 patent are valid and enforceable and have been infringed by GI, and that claims 7, 8, 23-27, and 29 of the '008 patent are invalid; we therefore affirm the judgment of the court regarding the '008 patent. Because we conclude that claims 1, 3, 4, and 6 of the '195 patent are invalid, we affirm the judgment concerning claims 4 and 6 and reverse the judgment concerning claims 1 and 3.

COSTS

Each party shall bear its own costs.

AFFIRMED-IN-PART, REVERSED-IN-PART, VACATED-IN-PART

Court of Appeals, Federal Circuit

Jurgens v. McKasy

Nos. 89-1645 and 90-1105

Decided March 7, 1991

JUDICIAL PRACTICE AND PROCEDURE

1. Procedure — Judicial review — Appealability (§410.4603)

Patent infringement defendants who failed to bring timely motion for directed verdict cannot challenge, on appeal, suffi-